REMARKS

Claims 40-43 are pending in the instant application. Claims 40-43 have been rejected. Claims 40-43 have been amended. Support for these amendments is provided in the specification at page 31-35. No new matter is added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims 40-43 under 35 U.S.C. 112, first paragraph

The rejection of claims 40-43 under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement has been maintained. In particular, the Examiner suggests that the claims as currently interpreted read on gene therapy. Further, the Examiner suggests that the specification has not provided a nexus between the working examples provided in the specification and a means of generating an immune response against said proto-oncogene claimed.

Applicants respectfully traverse this rejection.

At the outset, Applicants respectfully disagree with the Examiner that the claims "read on gene therapy".

The web site of the FDA (http://www.fda.gov/cber/infosheets/genezn.htm) provides the following definition of gene therapy:

WHAT IS HUMAN GENE THERAPY AND HOW DOES IT WORK?

Human gene therapy is the use of normal genes or genetic material to replace or cancel out the "bad" or defective genes in a person's body that are responsible for a disease or medical problem. The "good" genes find their way to the right spot in the body and begin to do the work required. The eventual hope is that for some diseases, like hemophilia, the good genes will keep working throughout a person's lifetime. There may be other uses of gene therapy, for example, to repair a wound, or to grow new blood vessels, during which the effect of the gene would only need to be active for a short time.

Advances in human gene therapy may allow doctors to treat a disease or abnormal medical condition by turning off a faulty gene and stopping the growth of a cancerous tumor, for example. Or they may allow the body to begin producing a necessary protein or other substance, such as an enzyme, that the faulty gene cannot order the body to produce.

For example, a person with the disease cystic fibrosis (CF) has a faulty gene for handling lung development, which results in excess mucous in the lungs, leading to chronic coughing, choking and serious respiratory infections. Cystic fibrosis patients often die young from pneumonia or other life-threatening respiratory diseases. The current median life span for CF patients is now about 30 years (see www.cff.org). For these persons, a doctor might inject a normal CF gene into a patient's bloodstream. The hope is that the CF gene would find its way into the patient's lungs, replace the faulty gene and help the patient's lungs to function properly.

The web site on the Human Genome Project (www.ornl.gov/hgmis) maintained by The US Department of Energy Office of Science defines gene therapy as follows:

What is gene therapy?

Gene therapy is a technique for correcting defective genes responsible for disease development. Researchers may use one of several approaches for correcting faulty genes:

- A normal gene may be inserted into a nonspecific location within the genome to replace a nonfunctional gene. This approach is most common.

- An abnormal gene could be swapped for a normal gene through homologous recombination.

- The abnormal gene could be repaired through selective reverse mutation, which returns the gene to its normal function.

- The regulation (the degree to which a gene is turned on or off) of a particular gene could be altered.

Neither of these definitions for gene therapy from well-established sources have anything whatsoever to do with the cellular immunogen of the present invention which is demonstrated to promote tumor regression by invoking an immune response. In no way is it taught, suggested or implied in the instant application that the claimed cellular immunogen replaces or cancels out a defective gene, is inserted in any manner into the genome of a host to which it is administered or that is regulates expression of a host gene.

Implicit to the concept of gene therapy is an engineered alteration to the genome of the host. In the present invention, the engineered alteration (by transfection of a transgene) is effected not with host cells but with allogeneic cells, i.e. donor cells isolated from a separate individual, such that there is no alteration to the

host genome and thus no host genome-mediated therapeutic effect can be ascribed. Furthermore, because donor allogeneic cells are by definition histo-incompatible with a recipient host, they would be rapidly destroyed by the host's immune system and thus could not subsume even an indirect therapeutic role, wherein transgene expression would continue to complement a defective host gene. Even in the very short-term, before the allogeneic cell destruction by the recipient host ensues, there could be no transgene expression-mediated complementation of the host proto-oncogene overexpression: i) such proto-oncogene overexpression is dominant for the transformed phenotype, even if the transgene were expressed in host tumor cells, but ii) in any case, the transgene is not expressed in host cells, let alone in host tumor cells. Instead, transgene expression would exert an anti-tumor effect by inducing an immune response that would target the proto-oncogene overexpressing tumor cells via recognition of shared determinants between the transgene and the proto-oncogene. In short, the fact that a "foreign" gene is expressed in a host does not ipso facto constitute gene therapy, but in the instant case recapitulates the history of vaccination and,

as such, would be recognized as vaccination and not gene therapy by both vaccinologists and gene therapists alike.

MPEP 2164.01(c) is clear; when a compound or composition claim is not limited by a recited use, the application is enabled for the claimed invention as long as any use is enabled, even in the event that multiple uses are disclosed. Examples set forth in the instant application at pages 44-54 teach one of skill in the art how to make and use the claimed invention to promote tumor regression. Thus, a use for the claimed invention is clearly enabled. Further enablement of additional uses, particularly a use such a gene therapy which is unrelated to the instant application, is therefore not required.

Further, Applicants disagree with the Examiner's suggestion that the specification has not provided a nexus between the working examples provided in the specification and a means of generating an immune response against said proto-oncogene claimed.

At the outset, it is respectfully pointed out that the claims are drawn to a cellular antigen that **promotes tumor regression**, not a "means of generating an immune response" as suggested by the Examiner. It is this claimed invention, a cellular immunogen that promotes tumor regression, which

must be enabled by the instant specification. See MPEP 2164.01.

The Examiner has established no reasonable basis as required by MPEP 2164.04, to question the enablement provided for the instant claimed invention. In fact, instead, in the Office Action mailed October 20, 2004, the Examiner acknowledged the specification to provide several working examples of the instant claimed invention, and in particular three plasmids which encode v-src. The Examiner acknowledged that these working examples disclose that the subcutaneous injection in wings of chicken with any of the three src expressing plasmids resulted in tumors which appear to spontaneously regress over time. The Examiner also acknowledged that the working examples demonstrate that injection of 100 μg of v-src plasmid followed 5 weeks later by a second injection of 200 μg of c-src plasmid resulted in a decrease in the percentage of chickens with palpable tumors compared to control animals. Thus, the specification, with its acknowledged working examples of three cellular immunogens, injection of which resulted in tumor regression over a period of weeks, clearly provides sufficient guidance to make and use cellular immunogens which promote tumor regression in a host as claimed.

Withdrawal of this rejection under 35 U.S.C. 112, first paragraph is therefore respectfully requested.

II. Rejection of Claims 40-43 under 35 U.S.C. 102(e)

The rejection of claims 40-43 under 35 U.S.C. 102(e) as being anticipated by Chada et al. (U.S. Patent 5,693,522) has been maintained. The Examiner suggests that because the instant claims do not specifically limit the sequences that are critical or essential for the transformation, the deletions as taught by Chada et al. are deemed to read on the "sequences of the transgene essential for the transformation" as claimed.

Applicants respectfully traverse this rejection.

At the outset, Applicants respectfully disagree with the Examiner's characterization of claims 40-43 as product-by-process claims. Claims 40 and 42 are product claims and are not limited by any specific process steps while claims 41 and 43 are method of production claims. In an earnest effort to clarify this point, Applicants have replaced the phrase "derived by" in claims 40 and 42 with --having--.

The products of claims 40 and 42 (and the methods as set forth in claims 41 and 43 for producing such products)

are structurally distinct from the purported anti-cancer immunotherapeutics of Chada et al.

In particular, the oncogene used in the vaccine by Chada is selected from the same species as the tumor-associate oncogene to be targeted. See e.g. the Abstract wherein Chada writes "---- a vector construct which directs the expression of at least one immunogenic, non-tumorigenic form of an altered cellular component normally associated with the selected tumor cells; since "alterations" of Chada et al. involve the engineering of point mutations at selected positions of the vaccine oncogene, Chada et al. are clearly talking about species identity in their choice of vaccine immunogen vis-à-vis the targeted oncogene.

In contrast, the cellular immunogens of the present invention are "cognate" to the targeted oncogene, which as defined in the specification, means that they are selected from a different species than that of the targeted oncogene, not from the same species as in Chada et al. This distinguishing structural difference is clear in the instant claims which are drawn to cellular immunogen comprising cells which are allogeneic with respect to the host and have been transfected with at least one vector comprising at

least one non-transforming transgene **cognate to a target proto-oncogene.**

Further, it is essential for the Chada vaccine that they insert point mutations, not randomly engineered, but rather incorporated at defined positions known to be "hot spots" for mutations that activate tumorigenicity. Thus, while there is recognized divergence in a cognate gene such as required in the present invention that can take the form of point mutations (often the divergence includes small deletions as well), these mutations appear randomly in the sequence and they are in no way linked to the tumorigenicity of the targeted oncogene.

In contrast, in the present invention, a deletion mutant is deliberately engineered into the cognate transgene which totally eliminates transformability and renders that cellular immunogen non-tumorigenic. Differences between a deletion mutant, as taught in the instant application, and point mutations, such as are taught by Chada, are outlined in the specification at page 30, line 23 through page 32, line 17; these differences include the possibility of a spontaneously arising back-mutation in the case of point mutations, but not in the case of a deletion mutant.

In an earnest effort to advance the prosecution of this case and to clarify distinctions between the present invention and cited art such as Chada et al., Applicants have amended the claims in accordance with teachings at page 30, line 23 though page 32, line 17 to state that the non-tumorigenic cellular immunogen comprises cells which are allogeneic with respect to the host and have been transfected with at least one vector comprising at least one non-transforming transgene **cognate to a target proto-oncogene** having a **deletion mutation** of a sequence of the transgene which totally eliminates transformability and consisting of **wild-type sequence outside the deletion mutation.** The invention, as claimed, is clearly a different product in no way structurally identical to that taught by Chada.

Withdrawal of this rejection under 35 U.S.C. 102(e) is therefore respectfully requested.

III. Rejection of Claims 40 and 42 under 35 U.S.C. 102(b)

The rejection of claims 40 and 42 under 35 U.S.C. 102(b) as being anticipated by Gelman et al. (Oncogene 1993):8(11):2995-3004) has been maintained. The Examiner states that "the cellular immunogen taught by Gelman et al.

is non-transforming, because Gelman et al. teach cell lines that are not capable of forming tumors, hence non-transforming". In particular, the Examiner cites table 1-cell line B (1702/c-csrc) of Gelman.

Applicants respectfully traverse this rejection.

At the outset, Applicants respectfully disagree with the Examiner's characterization of teachings in Table 1 that the construct of Gelman is non-transforming or non-tumorigenic. Table I shows a + for *Tumor formation* beside the cell line N (1702/c-src). Table 2 also shows strong tumor formation for B3T3/1702c-src cells (but of course none for B3T3neo cells). Furthermore, the 3rd sentence of the 3rd paragraph of Gelman et al explicitly states that "Our results indicate that murine cell lines expressing 1702src ---***induce tumors in syngeneic mice which regress***—". Accordingly, the teachings of Gelman, when read in their entirety as required by MPEP 2141.02, clearly contradict the Examiner's suggestion, i.e. that the construct of Gelman is non-transforming or non-tumorigenic.

It appears that the Examiner believes that a demonstration of one cell line not yielding tumors at the one cell dose tested implies that the transfecting transgene is non-transforming/non-tumorigenic, even though other

transfected lines were demonstrably transforming/ tumorigenic. Applicants respectfully disagree since the Examiner's suggestion, that one negative case (at the one cell dose tested) of tumor induction is dispositive, whereas several positive cases are not, is not the accepted understanding of tumorigenicity by those skilled in the art. Instead, the Examiner's perspective would be tantamount to saying that a gene that causes a tumor in one individual is "non-tumorigenic", on the basis that it did not cause a tumor in another individual. Such a view as the Examiner's is particularly problematic in the context of cancer vaccination, where an ever-present concern is an intrinsic tumorigenicity of the vaccine transgene itself. Few would likely accept vaccination if the transgene rendered even one cell line tumorigenic; in the Gelman case, of course, more than one cell line was rendered tumorigenic.

Moreover, the actual tumor regression disclosed by Gelman had nothing to do with any intrinsic transforming defect of the Gelman construct, but rather is a straightforward consequence of the immune response to src-specific determinants, as evidenced by the fact that Gelman teaches that "[s]ignificantly, the tumors induced by the

157src 1702src expressors in nude mice did not regress", whereas those induced in syngeneic non-nudes did.

However, in an earnest effort to advance the prosecution of this case, and to further distinguish structurally the instant claimed products from teachings such as Gelman, Applicants have amended the claims in accordance with teachings at page 32-35 to state that the cellular immunogen is **non-tumorigenic** and is comprised of cells which are allogeneic with respect to the host and transfected with at least one vector comprising at least one non-transforming transgene cognate to a target proto-oncogene having a deletion mutation in a sequence of the transgene required for transformation, said deletion mutation rendering the transgene **totally non-transforming.**

The construct of Gelman, demonstrated to be tumorigenic and to transform at least one host cell, is clearly distinguishable from the instant claimed invention.

Withdrawal of this rejection under 35 U.S.C. 102(b) is therefore respectfully requested.

IV. Conclusion

Applicants believe that this submission overcomes all pending rejections in this case and comprises a full and

complete response to the Office Action of record. Reconsideration and allowance of the pending claims is earnestly solicited in light of the above described amendments and remarks.

Respectfully submitted,

Kathleen A. Tyrrell
Registration No. 38,350

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LICATA & TYRRELL P.C.
66 E. Main Street
Marlton, New Jersey 08053

856-810-1515